NEW YORK HEART ASSOCIATION

ABSTRACTS OF PAPERS PRESENTED AT THE SCIENTIFIC SESSION ON RESEARCH, HELD AT HEART HOUSE, NEW YORK, N. Y., APRIL 28, 1970

*Hypersensitivity Reactions of the Heart: An Experimental Model**

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Electrocardiographic changes are relatively common in the immediate type of hypersensitivity reaction. Signs of altered generation and conduction of the cardiac impulse leading to arrhythmias have been reported. Ischemic changes, sometimes complicated by myocardial infarction, have also been reported.

An experimental model was developed to examine pathophysiological mechanisms involved, in the hope that this would lead to a therapeutic approach. Hearts of guinea pigs were passively sensitized *in vitro* by coronary perfusion with appropriate amounts of rabbit antiovalbumin. The hearts were then challenged with ovalbumin. Coronary effluents were collected and assayed for histamine content.

Sinus or nodal tachycardia and atrioventricular dissociation were invariably observed. Degree and duration of cardiac impairment correlated with the amounts of histamine concomitantly released by the heart. Electrocardiographic changes were always reversible, with the exception of few cases in which there was an irreversible reduction of the coronary flow. The cardiac effects of histamine released during the crisis of acute hypersensitivity could be reproduced on the sinus and atrioventricular nodes by the addition of histamine to the coronary circulation of nonsensitized hearts. Here too the effects were clearly correlated with the concentration of histamine.

This experimental model may prove to be a useful investigative tool in the treatment of cardiac arrhythmias caused by hypersensitivity reactions. *(Supported by the New York Heart Association.)*

*Dr. Levi's paper was selected by the Committee on the Scientific Session on Research of the New York Heart Association, to receive the Association's first annual J. Murray Steele Award, established in honor of the late J. Murray Steele, M.D., a director of the New York Heart Association, 1951-1964, for the best presentation before the Scientific Session on Research.

The Hypoxic Mammalian Heart: Metabolism and Hemodynamic Performance

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The metabolic and hemodynamic properties of the hypoxic myocardium probably play an important role in ischemic heart disease, especially in patients with an acute myocardial infarction where the peri-infarction tissue may be hypoxic; the ultimate fate of this hypoxic tissue and its contractile ability may significantly influence the morbidity, mortality, and complications which follow an infarction. For these reasons the biochemical and hemodynamic performance of isolated working rat hearts was studied under aerobic and hypoxic conditions with 5.5 mM. glucose or 5.5 mM. glucose + 0.4 mM. palmitate as substrate.

Peak aortic systolic pressure was higher ($p < 0.01$) when palmitate was present for both aerobic and hypoxic perfusions. Under aerobic conditions, the presence of palmitate decreased the uptake of glucose by 15% and the production of lactate by 41%. With hypoxia, there was a mean increase of glycolysis of 100%; nevertheless, the presence of palmitate decreased glucose uptake by 48% and lactate production by 36%. Total palmitate uptake was reduced 44% by hypoxia, and its oxidation to CO_2 was decreased by 80%. Incorporation of palmitate into tissue lipid was increased by 90%, primarily into the triglyceride fraction. The presence of palmitate decreased the utilization of carbohydrate under both aerobic and hypoxic conditions, but this effect was much greater under conditions of reduced oxygen availability.

The site of inhibition also varied with the amount of oxygen available. Under aerobic conditions, glycogenolysis was markedly reduced, but the uptake of glucose was only slightly inhibited; with hypoxia the converse situation obtained, and the uptake of glucose was markedly inhibited by the presence of palmitate, but there was no inhibition of glycogen breakdown.

The presence of palmitate decreased the hypoxic stimulation of glycolysis (Pasteur effect) and improved hemodynamic performance. This phenomenon may have therapeutic implications in protecting the hypoxic heart against lactic acidosis without diminishing the energy available for contraction.

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Myocardial Inceptive Excitability Threshold

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In contrast to the slow rise in excitability threshold in the first weeks of myocardial pacing, the threshold at the inception of pacing (I.T.) was found to fall rapidly. The I.T. was measured by use of a special stimulator with an accuracy of 0.01 mAmp. in patients undergoing placement of pacing catheters. Measurements were per-

formed in sinus rhythm, acute or chronic heart block in a supine, awake, and fasting state. In all instances threshold levels fell over the course of 200 to 300 sec. of pacing to stable, reproducible base levels less than 50% of the initial values. Variation in prepacing rhythm, pacing rate, reversal of polarity, or duration of stimulus did not influence the trend of the falling I.T., and the phenomenon was repeatable with the stimulating electrode in different myocardial sites.

Similarly, while the difference between stable base threshold and the energy required to recapture pacing from subthreshold levels (R.T.) was only 0.02 mAmp, the difference at inception of pacing was usually greater than 0.2 mAmp. R.T. at inception was in the order of twice I.T. but fell, with the same time course at I.T. The paradoxical responses of facilitated excitation were not due to mechanical damage to cellular membrane, as a 10-min. interruption in pacing allowed the I.T. to rise toward its initial level. Also, typical falls in I.T. could be elicited from catheters in position for hours without pacing. Similar falls were not excluded by high-energy stimuli delivered during the refractory phase in sequential-pacing experiments in animals. The response was considered due to electrically induced local changes in transmembrane ion gradients.

Clinical Experience and Hemodynamics with Synchronous Unidirectional Intraaortic Balloon Pumping in Medically Refractory Cardiogenic Shock

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Although the over-all mortality of myocardial infarction has improved, patients in whom cardiogenic shock supervenes still face an 85% to 100% mortality from progressive pump failure. Intra-aortic balloon pumping (IABP) currently appears to be the most effective mechanical heart assist through its ease of application and its effectiveness in decreasing left-ventricular work and increasing coronary blood flow. We have developed a dual-chambered balloon in which a spherical distal balloon initially inflates and occludes the aorta. This is sequentially followed by the inflation of a cylindrical proximal balloon in the same diastolic interval, which pumps blood entirely toward the aortic root. We have clearly shown in dogs that this unidirectional system results in a 50% greater increase in coronary blood flow over and above that obtained with an omnidirectional single-chambered balloon of equal displacement.

Our clinical experience to date includes three patients in medically refractory cardiogenic shock for an average of 44 hours prior to assist, with a systolic B.P. below 80 mm. Hg and an average cardiac index of 1.01 l/M^2. One has been discharged and is well; one was successfully assisted for 15 hours but extended his infarct and succumbed; the third was assisted for 16 hours, became hemodynamically stable, but subsequently died 42 hours postassist. In our comatose patients the sensorium cleared rapidly, central venous pressure fell promptly (average 10 cm. of H_2O), and the average hemolysis was 3.2 mg%. The maximum dp./dt. rose significantly (average 83%) while the presystolic ejection time decreased (average 36%), which suggested a definite improvement in ventricular performance. All hemodynamic data are stored in a memory bank for instantaneous recall, which permits a prospective assessment of the clinical course and of the proper time to initiate and terminate assistance in a patient under study.

Use of the dual-chambered balloon holds promise for reducing the mortality rate of refractory cardiogenic shock which complicates myocardial infarction.

Left Ventricular Volume and Function in Congenital Heart Disease

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Left ventricular end-diastolic (EDV) and end-systolic (ESV) volumes were measured in 6 normal children and 70 patients with congenital cardiac defects by use of biplane angiocardiography. The diagnoses included pure shunt lesions at atrial, ventricular, and pulmonary artery level, Fallot's tetralogy, pulmonary and aortic valvular stenosis, and mitral regurgitation. Stroke volume (SV) and ejection fraction (EF) were derived from measured volumes. Myocardial contractility index (MCI) was determined from left ventricular stroke work and EDV index. Patients with left-to-right shunts had above-normal EDV, ESV, and SV, which were greatest in ventricular defects and patent ductus. Fallot's tetralogy and mitral regurgitation also showed elevated values. Patients with semilunar valve stenosis fell within the normal range, though aortic stenosis tended to have longer volumes. Elevation of EF was present in shunt lesions but normal in all others except for Fallot's tetralogy, in which it was reduced. An inverse relation between ESV and EF existed for all entities, but for aortic stenosis, in which marked elevation was present, MCI was below normal. ESV, EDV, EF, and MCI were directly related to the severity of aortic stenosis. No correlation was found between age and any index measured. Cardiac rate was inversely related to EDV and SV in all but shunt-lesion patients. No correlation was noted between end-diastolic pressure (EDP) and volume measurements, though patients with aortic stenosis tended to have high EDP compared to Fallot's tetralogy, in which EDP was low.

Direct and Indirect Assessment of Left Ventricular Function in Coronary Artery Disease

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Left-ventricular (LV) performance is influenced by the extent of coronary artery disease (CAD). To evaluate the relation of indirect to direct measurement of LV function, 50 patients who had undergone LV and selective coronary angiography were subjected to left-ventricular end-diastolic pressure (LVEDP) correlated with indirect pre-ejection period (PEP) and left-ventricular ejection time (LVET). PEP and LVET were obtained from simultaneously recorded phonocardiogram, electrocardiogram, and external carotid pulse, and expressed in percentage of rate-corrected normal. Significant CAD was deemed present with $>$ 50% of lumen compromised. Pa-

tients were divided into groups: I, 3-vessel disease, 22 patients; II, 2-vessel disease, 12 patients; III, 1-vessel disease, 6 patients; IV, 0-vessel disease, 12 patients. LVEDP of Group I was significantly higher than that of III and IV ($p < 0.005$). PEP of Group I was significantly longer than that of III and IV ($p < 0.025$). LVET of Group I was significantly shorter than that of III and IV ($p < 0.05$). Correlation coefficient for PEP and LVEDP was $+0.57$ ($p < 0.001$). Presence and extent of CAD were found to influence direct and indirect assays of left ventricular function. *(Supported by USPHS Contract 43-67-1439, Myocardial Infarction Research Unit.)*

Noradrenergic Mediation of Cerebrovascular Spasm and Hypocapnic Vasoconstriction

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Previous investigations in our laboratory, that have utilized the catecholamine fluorescent technique have demonstrated the presence of an abundant noradrenergic periarterial fiber plexus in intracranial vessels of monkey and of man. Our study of experimental vascular spasm in monkeys has revealed a marked depletion of this catecholamine fluorescence after repeated spasm. This has suggested the possibility of noradrenergic mediation of cerebrovascular spasm. This hypothesis was tested in 26 normal and 2 sympathectomized monkeys, using catecholamines and their releasing and blocking agents. The effects of these agents on hypocapnic induced vascoconstriction were also studied. Fluorescent histochemical examination of the vessels was undertaken at the conclusion of each experiment after photographic documentation of changes in vessel caliber.

Data acquired from this study indicate that blood applied to the adventitia of the normal vessel consistently results in spasm. A reduction of arterial pCO_2 also results in severe constriction of the vessels. Alpha adrenergic blocking agents in the subarachnoid space 1) produce dilatation of blood-induced spastic vessels, 2) render a normal vessel incapable of spasm, and 3) result in arterial dilatation above normal caliber. Hypocapnic arterial constriction is removed by alpha-adrenergic blockade. The periarterial noradrenergic fiber plexus is depleted of its catecholamines by repeated spasm, catecholamine-releasing agents, and by surgical sympathectomy. The latter procedure, however, does not modify the ease of subsequent induction of spasm.

These data suggest that vascular spasm of the intracranial vessels is mediated at the noradrenergic receptor, and that blood contains an alpha adrenergic substance capable of acting at the receptor site. Alpha adrenergic blockade removes or prevents the appearance of blood-induced spasm. Further, it is postulated that the periarterial nerve fibers exert a significant tonic, constrictive effect on the cerebral vessels as their pharmacological removal or blockade results in a dilated vessel. Finally, adrenergic blockade of hypocapnic-induced vasoconstriction implies that CO_2-induced changes in cerebrovascular tone may be mediated through the noradrenergic system. *(Supported by a grant from the New York Heart Association and by an NIH Special Fellowship to Dr. Fraser [F112203-01] and NIH Grant 1-T01-NB-05618-02.)*

Hemodynamic Studies in Heroin-Induced Acute Pulmonary Edema

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Pulmonary edema has been recognized to occur during acute heroin overdose, but its mechanism has not been previously studied. Six young addicts with clinical and radiographic signs of pulmonary edema induced by heroin underwent cardiac catheterisation within 24 hours of onset of symptoms. The pulmonary capillary pressure was normal in all patients. The average pulmonary artery pressure was 32/13 mm. Hg (range 23/11 to 54/19). The level of pulmonary hypertension was proportional to the severity of the subject's hypoxemia; breathing 100% oxygen lowered the pulmonary artery pressure to the average value of 22/8 mm. Hg. Cardiac index and stroke-volume index were elevated to an average of 4.46 l/min./M^2 and 54 ml./beat/M^2 respectively. Pulmonary capillary blood volume, estimated from two-level diffusion capacity measurements, averaged twice the normal value (145 ml.) Arterial-oxygen tension averaged 62 mm. Hg during breathing of air and increased to 477 mm. Hg during 100% breathing of oxygen.

It is postulated that, in the absence of pulmonary-capillary hypertension, hypoxic vasoconstriction of pulmonary arterioles may be a mechanism of production of acute pulmonary edema. *(Supported by USPHS Grant HE-11840.)*

Fructose Absorption and Metabolism

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Fructose absorption was studied *in vitro* by employing rat intestinal rings incubated in a Krebs-Ringer buffer that contained C^{14}-fructose and measuring $C^{14}O_2$ production or radioactivity accumulation in the intestinal rings.

Over a 30-minute incubation, production of $C^{14}O_2$ increased linearly with the concentration of fructose substrate from 10^{-6} to 10^{-3}M. but this leveled off from 10^{-3} to 5×10^{-3}-M. Phlorizin (10^{-4}M.), 3-0-methylglucose (10^{-2}M.), and galactose (10^{-2}M.) did not depress the rate of $C^{14}O_2$ production. However, glucose (10^{-2}M.) cut $C^{14}O_2$ production by 50%.

The rate of entry of radioactivity into gut segments was linear over the initial 10 minutes when correction was made for the extracellular space by using H^3-methoxyinulin. Varying fructose concentrations from 10^{-5} to 5×10^{-2}M. elicited no saturation kinetics in the initial rate of uptake; adding 5×10^{-4}M. phlorizin or 10^{-2}M. glucose did not effect initial rates of uptake.

At 1 mM. fructose enters less than half as fast as glucose, galactose, or 3-0-methylglucose but more than twice as fast as sorbose. Adding 5×10^{-4}M. phlorizin retards the uptake of glucose, galactose, and 3-0-methylglucose to approximately the rate of sorbose entry while leaving the rate of the entry of fructose constant at double this common baseline rate for all other hexoses tested where the glucose-hexose carrier mechanism is rendered inoperative by phlorizin.

Some mechanism, perhaps carrier mediation, apparently augments passive diffusion for the absorption of fructose. This mechanism seems independant of the well-known glucose-galactose-hexose carrier system. Future studies must explain our failure to demonstrate saturation kinetics or competitive inhibition if this fructose-transport mechanism is to fit the contemporary carrier model.

Osmotic Effects of THAM

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One of the reasons advanced for the alleged superiority of THAM over $NaHCO_3$ for correction of acid-base disorders is that THAM, which lacks sodium and penetrates cells, will not produce osmotically induced redistribution of body water. This assumption has been tested directly in groups of 5 to 6 nephrectomized dogs given hyperosomotic infusions of either THAM or $NaHCO_3$ and in whom TBW (THO space) and plasma Pco_2 were maintained at essentially constant levels. Representative mean rises of ECF volume (Cl^{36} space) and plasma osmolality (Osm) one hour after completion of the infusions were as shown in the accompanying table.

These results demonstrate: 1) that hyperosmolar THAM produces major changes in ECF volume and osmolality whether it acts as a buffer (Group A) or not (Group B), and 2) that the magnitude of these changes are as great as those seen with an amount of $NaHCO_3$ (Group C), which provides greater buffering than THAM (Group A). Theoretically, these results are not unexpected; THAM at normal blood *p*H of 7.4 is 70% ionized and would be expected to exert 1.7 mOsm. per mM. administered while the total osmotic load of $NaHCO_3$ administered (2 mOsm./mM.) would be expected to decrease since, in buffering, some HCO^-_3 is converted to CO_2

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Group	*Infusion*	*ΔOsm.*	*ΔECF*
A	10 mM./kg. THAM (*p*H 8.5)	16.2 mOsm./kg. H_2O	11.3%
B	10 mM./kg. THAM (*p*H 7.3)	19.2 mOsm./kg. H_2O	13.1%
C	10 mM./kg. $NaHCO_3$	14.5 mOsm./kg. H_2O	8.6%
D	None (control)	3.4 mOsm./kg. H_2O	1.25%

Distensibility Characteristics of the Canine Pulmonary Artery in Vivo

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Pulmonary vascular compliance remains a point of dispute because significant changes in right ventricular output produce little change in pulmonary blood volume yet at the same time produce only minor changes in pulmonary-artery pressure. Knowledge of the *in vivo* volume-pressure (compliance) characteristics of the separate components of the bed might elucidate the apparent discrepancy. The present study evaluates the compliance of the pulmonary artery of intact anesthetized dogs, and relates it to other hemodynamic parameters.

In 9 dogs balloon catheters were introduced into one branch of the main pulmonary artery (MPA). Cardiac output was measured by the indicator dilution technique. Pulmonary-artery volume (PAV) and total pulmonary blood volume (PBV) were calculated from transit time of a radioactive indicator measured by appropriately collimated detectors over the heart-and-lung fields. Measurements were made during a control period and repeated during occlusion of one branch of the MPA, electrically induced hind-limb exercise, and exercise with unilateral occlusion.

Occlusion of one PA branch resulted in an average increase in flow through the opposite lung of 86%. PAV in the unoccluded bed rose markedly in 8 of the 9 animals ($m = +69\%$). Average compliance of the arteries was 18% of initial volume/mm. Hg P_{PA} (0.43 ml./ml. H_2O pressure). PAV varied directly with the $P_{PA_{diast}}$ ($r = 0.609$, $p < 0.01$). The data suggests decreasing compliance with increasing volume, but the trend is not statistically significant. Following unilateral PA occlusion the postarterial volume (PBV-PAV) in the opposite lung rose in 10 studies, fell in five and remained unchanged in 3. The postarterial volume varied inversely with $P_{PA_{diast}}$ and compliance appeared to decrease with $P_{PA_{diast}}$ but the trend was not statistically significant.

The present study confirms PA distensibility shown in isolated lungs. The data suggests that resistance to outflow from the arterial vessels is determined by vascular elements downstream whose distensibility determines the diastolic pressure in the PA, and whose volume is a significant portion of the total lung-blood volume.

The Mechanism of Oxygen-Induced Hypoventilation

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The present study investigates the mechanism of oxygen-induced hypoventilation (OIHV) in patients with respiratory insufficiency. Previous studies have not related this phenomenon to degree of hypoxemia, reduced co_2-responsiveness, or altered ventilatory mechanics.

Sixteen patients with obstructive pulmonary disease, alveolar-hypoventilation syndrome, obesity, or interstitial fibrosis were studied. The magnitude of OIHV was expressed as change in P_aco_2 from air control during 15 min. of breathing 100% o_2. Ventilatory response to co_2 ($\Delta Ve/\Delta P_aco_2$) was measured during breathing 5% co_2-in-air and 5% co_2-in-95% o_2.

Control P_ao_2 for all patients ranged from 31 to 95 mm. Hg, P_aco_2 from 35 to 72 mm. Hg, and maximum breathing capacity from 20 to 125% predicted. Although OIHV was observed in all patients with $P_ao_2 < 50$ mm. Hg, $P_aco_2 > 70$ mm. Hg, and maximum breathing capacity < 43% predicted, some patients with less severe respiratory insufficiency demonstrated OIHV.

The co_2-in-air response was not reduced in all patients with OIHV; however, the co_2-in-o_2 response was less than 0.4 l./min./mm. Hg in all patients who demonstrated this phenomenon.

Statistically significant correlation ($p < 0.001$) was demonstrated between the degree of OIHV and the ratio:

$$\frac{co_2\text{-in-}o_2 \text{ response}}{co_2\text{-in-air response}}$$

OIHV occurred in all patients in whom the co_2 drive that remained when hypoxemia was removed was less than 66% of the total drive as expressed by the ratio. In 4 patients restudied, improvement in the degree of OIHV related to an increase in this ratio.

The present study indicates that OIHV is related to the proportional contribution of hypoxemic drive to total ventilatory drive regardless of the degree of hypoxemia, magnitude of over-all drive, or etiology of respiratory insufficiency. *(Supported by Research Grant 8-0154-24 of the New York Heart Association.)*

Physiologic Predictors of Death in Acute Myocardial Infarction

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Since the advent of the specialized monitoring unit most deaths in hospitalized patients with acute infarction have resulted from refractory heart failure or shock. Current supportive treatment is often unsatisfactory and the mortality of cardiogenic shock is approximately 80%. Criteria are needed for the selection of patients at high risk in whom unconventional therapy such as mechanical circulatory support may be evaluated.

Ninety-eight studies have been performed in 35 patients from 5 to 239 hours after acute infarction. Hemodynamic measurements were well correlated with clinical findings. Mean cardiac index was 2.6 l./min./M.^{2} in patients with uncomplicated infarction (Clinical Class I), 2.4 l./min./M.^{2} in patients with congestive failure after infarction (Class II), and 1.0 l./min./M.^{2} in patients with shock following infarction. Corresponding stroke-volume indices were 33 ml./beat/M.^{2} in patients without complications; 30 ml./beat/M.^{2} in the presence of congestive failure, and 10 ml./beat/M.^{2} in the presence of cardiogenic shock. Mean left-ventricular end-diastolic pressure was 12 mm. Hg in Class I patients, 20 mm. Hg in Class II patients, and 22 mm. Hg in patients with shock. Hemodynamic measurements provided objective assessment of prognosis after myocardial infarction. Mean heart rate was significantly higher ($p < 0.005$), and cardiac index, stroke-volume index, cardiac and stroke work were significantly lower ($p < 0.005$) for each in patients who died as compared with those who survived. There was no significant difference in central blood volume, pulmonary arterial or left-ventricular end diastolic pressures between the two groups.

Analysis of data obtained during the initial physiologic study after admission to hospital for acute infarction indicates that certain measurements are predictive of death. Thus, cardiac work exceeded 3.0 kg.-m./min. in all survivors but was above this value in only 1 of the patients who eventually died. Similarly, stroke work was above 30 gm.-m./beat in all but 1 survivor and below this value in all but 2 of those who died. Only 6 of the 14 patients who died were in shock at the time of the initial study. Time of death varied from 5 hours to 2 months (median 30 hours) after the first physiologic measurements.

Cardiac and stroke work are derived from several variables and appear to be useful in identifying high-risk patients who may be candidates for unconventional therapy. *(Supported by USPHS Contract 43-67-1439, Myocardial Infarction Research Unit.)*

Oxygen Consumption of the Lung in Granulomatous Disease

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Studies in man with granulomatous pulmonary disorders have suggested that the diseased lung may utilize as much as 10% of the oxygen consumed by the body. Moreover, studies in dogs with induced pulmonary granulomas have given similar estimates when the dogs breathed room air, but smaller values when they breathed an hypoxic mixture. Since these *in vivo* estimates entailed a number of assumptions, we have examined the *in vitro* behavior of granulomatous lung tissue from rabbits prepared by intravenous injections of complete Freund's adjuvant after the method of Moore and Schoenberg *(Brit. J. Exper. Path. 45*:488, 1964). At the height of the disease the rabbits were sacrificed, the pulmonary artery was rinsed with saline, and adjacent aliquots of the lung were taken for pathologic and metabolic study. Morphometric measurement showed that, on the average, 92% of the lung consisted of granulomata. Chopped tissue slices were suspended in Krebs Ringer solution equilibrated with oxygen tension over a range of 10 to 240 mm. Hg and the oxygen consumed was measured by use of a Yellow Springs Instrument Oxygen Monitor System. The aliquot was then analyzed for soluble protein content. At an oxygen tension of 150 mm. Hg, the specimens from 10 diseased rabbits utilized, on the average, 9.4 $\pm$ 1.6 μl. O_2/mg. protein/hr. compared to a value of 6.3 $\pm$ 0.6 in 10 controls (DF $=$ 18; t $=$ 5.8; $p < 0.001$). The larger respiratory rate of the granulomatous tissue, coupled with the fact that the abnormal lungs were four times heavier than the controls, support the observations in men and dogs that the oxygen utilized by diseased lung may be appreciably increased. Also, at oxygen tensions below 100 mm. Hg the *in vitro* respitory rate of lung tissue fell linearly with reduction in equilibrating tension. While this behavior resembles that seen in diseased dogs *in vivo,* the mechanism of the fall in respiration in both systems remain unexplained. *(Supported by USPHS HE-05741, HE-02001, and HE-5443.)*

The Reversibility of Postischemic Myocardial Contractile Failure by High-Energy Phosphates

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The effects of ATP and ADP infusion on contractile force development by normal and postischemic myocardium were studied. The preparation was the isometrically contracting *in situ* feline right ventricular papillary muscle perfused with oxygenated Tyrode solution that contained 4% low MW dextran, by Langendorff technique at 23° to 27° C. Hearts were paced at regular rates. After obtaining control contractile force at optimal muscle-length coronary flow was stopped for 20 to 30 minutes. Contractile force fell and arrhythmia usually occurred. Resumption of perfusion with Tyrode solution resulted in rise in contractile force to 30 to 60% of control. After a steady state was reached, 0.5 mM. ATP in Tyrode solution was infused for 3 to 5 minutes. The contractile force increased to 60 to 100% of control. When 0.5 mM. ADP was infused through muscles in postischemic state, contractile force increased only to 30 to 40% of control. If 0.5 mM. ATP was then infused through the same muscles, contractile force increased to 60 to 90% of control.

Fluorodinitrobenzene (FDNB) inhibits intracellular resynthesis of ATP from creatine phosphate and ADP. When 0.38 mM. FDNB in glucose-deficient Tyrode solution was infused, contractile force showed a gradual fall to the point of cardiac standstill. If perfusion with Tyrode solution was resumed when contractile force had decreased to 50% of control, force continued to fall slowly or remained stable. Infusion of 0.5 mM. ATP in Tyrode solution without glucose resulted in increase in contractile force to 70 to 100% of control. When ADP was infused to the FDNB-treated preparation, contractile force either decreased further to 18 to 20% of control or increased slightly.

In the postischemic papillary muscle ATP appears to be capable of entering the cell and of providing energy for contraction. The manner by which it enters is uncertain at present, as is the existence of a possible secondary action upon the membrane transport system. *(Supported by the U.S. Veterans Administration and the New York Heart Association.)*

Muramidase Excretion in Nephrotic Syndrome

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Muramidase excretion has been used as an indicator of low-molecular-weight protein excretion in renal disease. In this study 31 patients with nephrotic syndrome secondary to lipoid nephrosis, membranous, and proliferative glomerulonephritis were studied. Muramidase determinations were performed on both serum and urine of all patients. Muramidase excretion differed in the three groups of patients. Five patients with lipoid nephrosis, all with normal renal function, had little or no muramidase in the urine and the serum levels were normal. Five of 9 patients with membranous glomerulonephritis had increased urine muramidase concentrations, 4 of these had abnormally high serum values; all 5 patients had impaired renal function. Eight of 16 patients with proliferative glomerulonephritis had elevated muramidase concentrations in urine, and 4 of these had high serum concentrations. Six of these patients had serum creatinine concentrations above 1.3 mg.%.

It is concluded from these observations: 1) that the serum concentrations of muramidase increase with impairment of renal function, and that a direct correlation can be established between serum concentrations of muramidase and creatinine; 2) that there is no correlation between serum concentration and urinary excretion which suggests that defective tubular reabsorption of low-molecular-weight proteins is causing the appearance of muramidase in the urine; 3) that muramidase concentration in the urine is independent of total excretion of protein since several patients with massive proteinuria excreted only trace amounts of muramidase.

In summary: poor correlation between muramidase concentration in serum and urinary-excretion rate seems to favor the concept that reduced tubular reabsorption is the cause for increased muramidase excretion. *(Supported in part by grant 5 RO1 AM05009 from the National Institutes of Health.)*

*Fellow of the New York Heart Association.

In Vivo *Hemodynamic Comparison of Mitral Valve Prostheses*

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Analysis of the hemodynamic performance of the natural mitral valve and five low-profile mitral prostheses has been undertaken by use of our technique of rapid valve exchange. Sixteen experiments in five dogs were performed over a wide range of flow rates. A-V pressure gradients were recorded simultaneously with the instantaneous mitral flow obtained with an intracardiac electromagnetic flow probe sutured supravalvularly.

In addition to the standard calculation of effective orifice areas, we have also selected parameters and techniques of data analysis which emphasize the dynamic characteristics of the valve-fluid system, i.e., the timing between gradient and flow events including the timing and contribu-

tion from atrial contraction. The valves performed as shown in the table below.

Several other observations are worth noting. Atrial contraction before the peak of early diastolic filling adds little to the filling volume; after the peak it adds as much as 25 to 30% more volume. All the valves responded to augmented filling due to atrial contraction in the same manner as the natural valve. Each valve permitted a filling volume sufficient to maintain the cardiac output. The filling volume was limited by the time of atrial contraction and the magnitude and rate of change of the pressure gradient. The inertia of the blood as it flows from the pulmonary veins through the atrium and into the ventricle allows the flow to continue after the gradient has reversed. The observation in both the natural and prosthetic valve that flow starts immediately upon reversal of the gradient can best be explained by the inertia of pulmonary inflow, and an actively relaxing ventricle.

EFFECTIVE ORIFICE AREA AS A PER CENT OF THE EFFECTIVE AREA OF THE ECCENTRIC MONOCUSP VALVE— BASED ON PEAK AND TEMPORAL-MEAN PRESSURES AND FLOWS

	Peak values	*Mean values*	*Average of peak and mean*
Eccentric monocusp	100	100	100
Capetown	83	62	73
Kay-Shiley	74	67	71
Cross-Jones	88	74	81
Wada	80	74	77

Hypoxemia-Induced Pulmonary Edema

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The role of acute hypoxemia in the production of pulmonary edema was studied in seven dogs under pentobarbital anesthesia. Extravascular lung-water volumes were calculated from indicator dilution measurements of labeled red cells, albumin, and water during air breathing and during one hour of 5% oxygen breathing. Serial blood samples were analyzed for whole-blood histamine and plasma-serotonin levels. Pulmonary arterial, pulmonary-artery wedge, left atrial and systemic pressures, pulmonary vascular resistance, pulmonary compliance, and airway resistance were determined throughout the experiments. Wet/dry lung-weight ratios and histological findings were compared.

The volume of extravascular lung water increased by at least 50% in three dogs and did not change in four. Pulmonary artery pressure increased in all dogs from an average of 35/15 to 57/23 mm. Hg; the largest increase in extravascular lung water was observed in the dog with the highest elevation of pulmonary artery pressure. Pulmonary-capillary pressure remained unchanged. Pulmonary vascular resistance averaged 215 dynes•sec•cm.$^{-5}$ during air breathing and 222 dynes•sec•cm.$^{-5}$ during hypoxemia. Histamine and serotonin levels decreased during hypoxemia from 0.029 to 0.022 μg./ml. and from 0.12 to 0.09 μg./ml. respectively. In the absence of pulmonary capillary hypertension, hypoxic vasoconstriction of pulmonary arterioles may be a mechanism of production of acute pulmonary edema. *(Supported by USPHS Grant HE-11840.)*

Thyrotoxicosis and Reversal of the Electron Transport in Cardiac Mitochondria

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Rabbit-ventricle mitochondria (Mc) isolated and assayed identically, exhibited two alternative "succinate-linked" kinetic characteristics: I) ATP-dependent electron-transport reversal and respiratory control (RC) by ATP; II) no ATP requirement for rapid reversal of electron transport and no RC by ATP. The controlled and active state QO_2's in II were 50 to 100% higher than in I. One minute of preincubation of Mc yielded these kinetic conversions:

$$\text{(I)}\quad \frac{\text{200 } \mu\text{M pyruvate, or 40 } \mu\text{M octanoate, or 2.5 mM CSA}}{\text{50 } \mu\text{M oxaloacetate, or 2.5 mM L-malate}}\quad \text{(II)}$$

These and other results strongly suggest that under specific conditions the "substrate-level" events can greatly affect the apparent coupling of oxidative phosphorylation, and that oxaloacetate may regulate not only the oxidation of succinate and the reduction of mitochondrial pyridine nucleotides (as evidenced by other workers), but it can affect the state-4 rate as well as the respiratory control by ATP (phosphate potential).

Kinetics (II) were most readily obtained after *in vivo* thyroxine treatment (20 μg. T_4 injected per 100 gm. body weight per day for four days). As the recent evidence for loose coupling by *in vivo* administered T_4 rests mainly on respiratory measurements performed under conditions closely similar to those here employed, the aforementioned effect represents a mechanism that may resolve the current controversy in the literature pertinent to the effect of *in vivo* thyroxine on oxidative phosphorylation. *(Supported by USPHS Research Grant 5 RO1 HEO 4413-08.)*

Kinetics of Lidocaine in Blood

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The pharmacodynamics of lidocaine depend on the method of administration. Previous studies with constant infusion suggest that blood levels reach a plateau after 30 to 60 min. Twelve patients in sinus rhythm were infused with lidocaine for 24 hours at a rate of 30 μg./kg./min. Blood samples were assayed at frequent intervals during infusion and for 12 hours thereafter. Mean blood concentration approached a constant level only after 8 to 12 hours. Blood level after discontinuation of infusion fell

exponentially with $t_{1/2}$ of 105 min. The rate of cumulation after onset of infusion and this metabolic decay are the same. Single IV doses of 0.5, 1.0, and 2.0 mg./kg. were given to 40 patients. Three exponentials comprise the decay curve. The first, $t_{1/2}$ = 8.5 min., reflects distribution out of intravascular compartment. The second, $t_{1/2}$ = 30 min., represents redistribution to total body water and some fat depots. This was conformed by the calculated volume of distribution. The third segment, $t_{1/2}$ = 120 min., agrees with the metabolic half-life observed after infusion. Although antiarrhythmic action may persist for 10 to 30 min. after a single dose, the duration of activity does not correlate with "therapeutic" blood levels of 2 to 5 μg./ml. reported from infusion studies. This discrepancy reflects the lack of a steady-state equilibrium after a single injection. *(Supported by USPHS Contract 43-67-1439, Myocardial Infarction Research Unit.)*

Magnesium-Ion Inhibition of Renovascular Constriction

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Previous experiments had demonstrated magnesium-ion (MG^{++}) inhibition of kalemic and catecholamine-induced vasoconstriction of the mesenteric artery. The effectiveness of this cationic blockade prompted a study of renovascular responses to regional infusions of Mg^{++} in the presence of local and generalized peripheral vasoconstriction. Noncannulating flow probes were placed about the renal arteries, and the ureters were individually catheterized in 30 dogs. Bolus or continuous infusions of Mg^{++} (50% $MgSO_4 \cdot 7H_2$) – 4 mEq. $Mg.^{++}$/ml.) were delivered via the renal artery while the other kidney served as a control. Simultaneous injections of graded amounts of Mg^{++} and epinephrine, norepinephrine and neosynephrine were made to evaluate cation inhibition of renal vasoconstriction. Bilateral renal blood flows, urine volumes, and sodium excretions were measured during the selective infusion of Mg^{++} before and after hemorrhage and intravenous catecholamines. In a representative study 1.5, 3.5, and 6 mEq. of Mg^{++} neutralized renal-artery constriction by 1.6 μg. of neosynephrine, norepinephrine, and epinephrine respectively. Arterial infusion of Mg^{++} (0.8 mEq./min.) upon completion of the surgical preparation produced an increase in blood flow, urine volume, and natriuresis by mean factors of 1.4, 9, and 12 respectively compared with controls. Before or after intravenous catecholamines and hemorrhage Mg^{++} infusion prevented or reversed the depression of renal function noted in the untreated kidney; neutralization ceased within 10 min. of discontinuing the infusion. Our findings suggest that regional instillation of Mg^{++} neutralizes or reverses sympathetic renal vasoconstriction of pharmacologic or endogenous origin. The cation blockade appears to be rapid in onset, of brief duration and concentration dependent. *(Supported by Grant FR-00503 from USPHS, and a grant from G. D. Searle & Co.)*

Vasodilator Effect of Papaverine and Phosphodiesterase Activity

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We have reported evidence that indicates that the adenyl cyclase (AC)-phosphodiesterase (PDE) system which regulates intracellular cyclic-AMP participates in the regulation of uterine muscle tone and contractility. These experiments were designed to investigate the role of this system in the regulation of vascular smooth-muscle tone and contractility. AC and PDE activity was assayed in rabbit aorta and the vascular responses to drugs which act on these enzymes were studied. It was first shown that papaverine (P) inhibits PDE activity. This inhibitory action of P (K_i about 10^{-5} M.) is more than 10 times greater than that of theophylline (T). T and P decreased aorta-strip contraction caused by epinephprine (E), norepinephrine, and phenylephrine. When the effect of T or P was simulated by the addition of dibutyryl cyclic-AMP (2×10^{-3} M.), the contractile response was decreased by approximately 90%. These results support the concept that intracellular cyclic-AMP participates in the regulation of vascular tone and reactivity: higher levels decrease and lower levels seem to increase the contractility. The effect of P seems to be related to the inhibition of PDE, which results in an increased level of cyclic-AMP in the cell. This mechanism of action of papaverine was studied in other systems regulated by cyclic-AMP. In striated muscle P (5×10^{-4} M.) decreased glycogen content to the same extent as E (10^{-5} M.): from a control concentration of 5.96 μg./mg. dry weight to 3.31 μg. and 3.37 μg., respectively. Both drugs when combined produced an additive effect; they decreased muscle glycogen to 1.86 μg./mg. dry weight. In adipose tissue papaverine (10^{-4} M.) increased E (10^{-5} M.)-induced lipolysis (from 6.21 to 8.15 glycerol μm./gm. of tissue). These results and the direct measurements of PDE activity demonstrate the inhibitory action of P on this enzyme. The vasodilatory effect of papaverine appears to be exerted through this mechanism. *(Supported in part by the Bob and Dolores Hope Gift for the Study of Shock.)*

*A senior investigator of the New York Heart Association.